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Sung-Yun Kwon

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EXAMINER

GHALI, ISIS A D

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**MAILED**  
**MAY 19 2006**  
**GROUP 1600**

**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

Application Number: 09/489,088  
Filing Date: January 21, 2000  
Appellant(s): KWON ET AL.

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VID MOHAN-RAM  
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed March 03, 2006 appealing from the Office action mailed April 21, 2005.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct. Claims 33-40 were withdrawn from consideration in response to Restriction Requirement dated March 30, 2001. Claims 2, 4, 6, 8-10 and 19 are canceled.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct. Amendment after final has been entered. Claims 1 and 22 have been mended and claims 2, 4, 6, and 8-10 have been canceled. However, upon further review, claims 26-30 found to be dependent on canceled claims 4, 6, 8, 9, and 10. Therefore, the examiner contacted the attorney, Mr. Vid Mohan-Ram, on May 09, 2006, to correct the improper dependency of the claims to expedite the prosecution. Mr. Mohan-Ram corrected the dependency of claim 26 to claim 3 instead of claim 4, canceled claimed 27 and 28, corrected the dependency of claim 29 to claim 26 instead

Art Unit: 1615

of claim 6, and corrected the dependency of claim 30 to claim 1 instead of claim 8.

Therefore, claims 1, 3, 5, 7, 11-18, 20-26, 29-32 are in the appeal.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

5,630,796	BELLHOUSE	5-1997
WO 98/29134	TECHNOLOGIES, INC.	7-1998

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 3, 5, 7, 11-18, and 20-26, 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/29134 ('134) in view of US 5,630,796 ('796).

WO '134 teaches a method of enhancing the permeability of a permeant (active agent) across of a biological membrane including skin or mucosa utilizing microporation of the membrane at the site of administration, followed by contacting the porated surface by the active agent and a permeation enhancer (abstract; page 9, lines 5-10; page 10, line 8; page 15, line 14; page 19, lines 6-15; page 34, lines 5-9; page 100, lines 14-16). The active agent includes polypeptide and vaccine associated with a carrier such as microcapsules or microparticles (page 14, lines 19-25; page 15, lines 1-4; page 29, line 11). The micropores should not be smaller than 1 micron in diameter (page 25, lines 3-4). The pores can be covered by transdermal patch to deliver the active agent through the skin (page 118, Example 50). The reference suggests forming the pores using any non-invasive means that do not require entry of needle to the skin or mucosa or invasive instruments (page 32, lines 10-11).

WO '134, however, does not teach the needleless syringe used to form the skin pores, but suggests forming the pores using any non-invasive means that do not require entry of needle to the skin or mucosa or invasive instruments.

US '796 teaches a noninvasive method comprising needleless syringe for effective transdermal delivery of particles containing a therapeutic agent. The needleless method provides safe quick method with less pain and no risk of infection. The active agents include viruses or proteins (antigen), insulin with a carrier (adjuvant) or a placebo. Injection velocities may be between 200 up to 3000 m/sec. and the particle size ranges from 0.1 to 250 micrometer. The particles can be made from metal. The drug particles can be encapsulated. More than one therapeutic agent can be

Art Unit: 1615

injected together. See the abstract, col.1, lines 61-63; col.2, lines 30-37; col.4, lines 1-23, 40-55; col.8, lines 17-20; col.10, example 2.

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to provide a method for administering a therapeutic agent to the skin or mucosa comprising forming pores in the skin or mucosa using noninvasive means followed by topical application of the active agent by a patch as disclosed by WO '134, and use the noninvasive needleless syringe disclosed by US '796 to form the skin pores, motivated by the teaching of US '796 that the needleless method is safe quick method with less pain and no risk of infection, with reasonable expectation of having a method for delivery of active agents across the skin or mucosa comprising porating the skin with needleless syringe followed by application of a topical device such a method accelerates the drug delivery through the skin or mucosa to the systemic circulation safely and quickly with no pain.

#### **(10) Response to Argument**

Appellants' arguments filed 03/03/2006 have been fully considered but they are not persuasive.

Appellants traverse the rejection of claim 1, 3, 5, 7, 11-18 and 20-26, 29-32 under U.S.C. 103 (a) as being unpatentable over WO '134 in view of US '796.

##### **1. Examiner's Basis for the Rejection**

Claims 1, 3, 5, 7, 11-18, and 20-26 and 29-32 stand rejected as allegedly obvious over WO 98/29134 (Eppstein) in view of United States Patent No. 5,630,796

Art Unit: 1615

(Bellhouse). Appellants herein addresses the ground of rejection as set forth in the previous office action and presents the following arguments:

2. **The combined teachings of Eppstein and Bellhouse do not Teach or Suggest Each and Every Limitation of the Claimed Invention**

Appellants argue that the examiner has failed to establish a *prima facie* case of obviousness because the combined teachings of Eppstein and Bellhouse do not teach or suggest each and every limitation of the claimed invention. Eppstein relates to a method where a surface is prepared by microporation for subsequent administration of a therapeutic agent. The method of Eppstein involves two-step process. Firstly, a biological membrane is prepared for the administration of a therapeutic agent by microporation, and secondly, the biological membrane which has been prepared in this way is contacted with a therapeutic agent and permeation enhancer. In contrast, amended claim 1 is directed to a method for enhancing the flux or improving the uptake of a therapeutic agent which is administered at the same time that microporation takes place. After the therapeutic agent has been administered, a transdermal delivery device or an occlusive dressing is positioned over the area of skin or mucosa which has been microporated and to which the therapeutic agent has (already) been administered. Examples 1-4 demonstrate how the flux of therapeutic agents administered using a needleless syringe may be enhanced using an occlusive dressing. In each of these examples, the therapeutic agent is administered at the same time as microporation

Art Unit: 1615

takes place and the application of an occlusive dressing takes place subsequent to administration of the therapeutic agent/microporation.

In response to this argument, the examiner is pointing out to the scope of the present claims which is method for transdermal drug delivery comprising two steps, first is accelerating particles containing therapeutic agent into or across area of skin, and second is positioning a transdermal drug delivery device to the site the delivery of a therapeutic agent over that area of skin. Eppstein teaches enhancing the trans-membrane (skin or mucosa) flux rate of a drug into a selected area achieved by method including two steps, first step of minimally invasive or non-invasively making micropores to the membranes (abstract; page 7, lines 18-20), followed by second step of applying transdermal drug delivery device. Eppstein defines "non-invasive" by: "means not requiring the entry of a needle" (page 32 ,line 10-11). Therefore, the reference teaches non-invasive needleless formation of micropores to deliver therapeutic agents into or across the skin or mucosa to accelerate the delivery of the transdermal therapeutic agent that is applied subsequently from a transdermal delivery device. Eppstein teaches high-pressure jet fluid to make the perforation, which reads on particles at high speed. The difference between the present claims and Eppstein reference is that Eppstein does not teach particles forming the pores that comprise therapeutic agents. Bellhouse is relied upon for teaching delivering particles comprising therapeutic agents to form pores of the skin caused by needleless syringes. Bellhouse teaches the one step method for delivering the therapeutic agent and porating the skin, but does not teach

Art Unit: 1615

the step of positioning an occlusive dressing or transdermal delivery device over the site of drug delivery. The combination of Eppstein and Bellhouse teach the two steps of the claimed process. Therefore, Eppstein recognized method for transdermal drug delivery by making micropores to the skin without the use of needle, followed by application of a transdermal drug delivery device and Bellhouse teaches the use of particles comprising therapeutic agent and needleless syringe to make the micropores because it is safe and painless. Therefore, one having ordinary skill in the art would have been motivated to combine the teaching of the Eppstein that teaches perforating the skin non-invasively before application of transdermal drug delivery device with the teaching of Bellhouse that teaches non-invasive method for perforating the skin that meanwhile delivers active agent to the skin to enhance delivery of active agents to the skin during skin perforation followed by booster dose of the therapeutic agent to achieve continuous prolonged delivery of the therapeutic agent to the patient in need of such treatment. Regarding the appellants' argument that the examples show enhancement of drug delivery using occlusive dressing subsequent to the needleless drug deliver, appellants' attention is drawn to the scope of the claims that are not limited to occlusive dressing but encompass transdermal drug delivery device.

### **3. Eppstein Teaches Away from the Method of Claim 1**

Appellants argue that Eppstein teaches away from the claimed invention because Eppstein teaches that microporation and the administration of a therapeutic agent are two separate steps that must be carried out sequentially. Furthermore, the

Art Unit: 1615

active agents that may be used in the method described by Eppstein include polypeptides and vaccines, optionally associated with a carrier comprises liposomes, lipid complexes, microparticles that are not particles intended for use with a needleless syringe because such particles do not have the necessary strength to withstand the forces associated with delivery from a needleless syringe. This may be contrasted with the particles used in Example 1 of the present application wherein the particulate insulin formulation prepared using specific steps (lyophilisation, compression and milling) so as to ensure that the density of the particles is high enough for transdermal/transmucosal delivery at supersonic velocities. There is no suggestion in Eppstein that such steps should be taken. Therefore, it does not appear to be possible to use the particles in Eppstein with a needleless syringe.

In response to these argument, the examiner is pointing out to *In re Freed* 425 F.2d 785, 165 USPQ 519 (CCPA 1970); and *Fromson v. Advance Offset Plate Inc.*, 775 F.2d 1549, 225 USPQ 26 (Fed.Cir. 1985) wherein it was found obvious to use one step method instead of two steps of the prior art because it is merely a matter of obvious technical choice. Therefore, Eppstein by teaching two step method is not teaching away from the method of claim 1 that requires one step method because the enhanced delivery of therapeutic active agent is achieved by the method of Eppstein. With regard to the argument that the microparticles of the prior art can not used for the claimed method because the particles of the claimed method are produced by a specific method, the examiner is pointing out to the scope of the claims wherein no specific

Art Unit: 1615

particles are claimed or method of their production. The particles disclosed by Eppstein withstand the sonic energy as disclosed on page 15, line 13 of Eppstein publication.

Eppstein further suggested the needleless syringe on page 32, line 10. In addition, the particles that can stand the supersonic velocities are disclosed by Bellhouse, and one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The combined teachings of Eppstein and Bellhouse teach the present invention. The test for obviousness is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

4. **A Person of Ordinary Skill in the Art Would Not Have Been Motivated to Combine the Teachings of Eppstein and Bellhouse**

Appellants argue that a person of ordinary skill in the art would have not been motivated to combine the teachings of Eppstein and Bellhouse to arrive at the claimed invention because Bellhouse teaches that the needleless method is "a safe and quick method with less pain and no risk of infection."

In response to this argument, the examiner position is that the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve different problem. It is not necessary that the prior art

Art Unit: 1615

suggest the combination or modification to achieve the same advantage or result discovered by applicant. *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972).

Appellant argue that the Examiner has failed to establish a *prima facie* case of obvious because the combination of Eppstein and Bellhouse does not teach each and every limitation of the claimed invention, and a person of ordinary skill in the art would not have been motivated to combine the teachings of Eppstein and Bellhouse for the reasons discussed below:

(a) **Bellhouse teaches that the disclosed method should not be combined with other methods**

Bellhouse teaches that the disclosed method should not be combined with other methods to col.1, lines 45 to 48, explains that the needleless syringe is "useful for routine delivery of drugs, such as insulin..., and could be of use in mass immunization programs, or for the delivery of slow release drugs such as pain killers and contraceptives". Thus, Bellhouse makes it clear that the needleless syringe is useful merely for the routine delivery of drugs and cannot reasonably be expected to be of use in a multi-step drug delivery technique, such as the method of claim 1, in which different drug delivery technologies are used to custom tailor drug delivery profiles. Therefore, Bellhouse would not have motivated a skilled artisan to combine its teachings with the teachings of Eppstein.

In response to this argument, Bellhouse does not teach anywhere that this method cannot be combined by any other method. In considering the disclosure of the

Art Unit: 1615

reference, it is proper to take into account not only the specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom. *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968). The rational to modify or to combine the prior art does not have to be expressly stated in the prior art; the rational may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art. The multi-step method is taught by Eppstein including porating the skin and applying transdermal patch, and Bellhouse is relied upon for teaching the first step of the method for porating the skin by particles containing therapeutic agent that step can replace the step of porating skin disclosed by Eppstein. The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve different problem. It is not necessary that the prior art suggest the combination or modification to achieve the same advantage or result discovered by applicant. *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972). In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Eppstein teaches the multi-step process to enhance delivery of active agent, first step of making micropores using

Art Unit: 1615

non-invasive needleless method, and second step of applying transdermal device comprising the active agent; and Bellhouse is relied upon for teaching a needleless painless method for making the micropores which at the same time can deliver active agents. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to provide a method for administering a therapeutic agent to the skin or mucosa comprising forming pores in the skin or mucosa using noninvasive means followed by topical application therapeutic agents by a patch, and use the noninvasive needleless syringe that deliver particles that also contain therapeutic agent to make the micropores to achieve enhanced delivery of the therapeutics. Motivation arises from the teaching of Bellhouse that the needleless method is safe quick method with less pain and no risk of infection that meanwhile could deliver active agent as it forms the micropores, with reasonable expectation of having a method for delivery of active agents across the skin or mucosa comprising porating the skin with needleless syringe that deliver particles containing active agents followed by application of a topical device such a method accelerates the drug delivery through the skin or mucosa to the systemic circulation safely and quickly with no pain.

**(b) Eppstein does not teach or suggest the use of particles administered via needleless syringe**

Appellants argue that Eppstein does not teach or suggest the use of particles administered via a needleless syringe. Appellants argue that the non-invasive technique described at page 32, lines 10 to 11 of Eppstein reference defines the term “non-invasive” as “not requiring the entry of a needle, catheter, or other invasive instrument

Art Unit: 1615

into the skin or mucous membrane.” However, this portion of the Eppstein document does not teach or suggest that “any” non-invasive technique may be employed with the described method. In fact, Eppstein only discloses five methods of porating a biological membrane, none of which utilize the needleless injection technique taught by Bellhouse. Eppstein does mention the use of a high pressure jet of fluid, but not using a fluid to propel a particle across the biological membrane as would be the case with a needleless syringe. Moreover, although five types of poration are referred to in the description of Eppstein, in reality, an even smaller number of specific types of poration is supported by the Examples of Eppstein. Yet again, this emphasizes the fact that there is simply nothing in Eppstein which teaches or suggests the needleless injection technique taught in Bellhouse.

In response to these argument, appellant admit that Eppstein teaches “non-invasive” as “not requiring needle”, page 32, lines 10-11 of Eppstein reference. Further, and unlike appellant assertion, on page 7, lines 18-20, Eppstein discloses “method of non-invasively enhancing the trans-membrane flux rate of a drug”. Hence, Eppstein teaches non-invasive method to enhance the delivery of drugs across biological membranes, and teaches methods that do not require needles, i.e. needleless. Bellhouse is relied upon to show that the specific claimed method of porating the skin was known in the art at the time of the invention, i.e. using needleless injection technique by high pressure jet of fluid containing particle containing active agents. The disclosed examples and preferred embodiment do not constitute a teaching away from

Art Unit: 1615

a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The test for obviousness is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). A conclusion of obviousness under 35 U.S.C. 103 (a) does not require absolute predictability, only a reasonable expectation of success; and references are evaluated by what they suggest to one versed in the art, rather than by their specific disclosure. *In re Bozek*, 163 USPQ 545 (CCPA 1969).

(c) **The references fail to provide a teaching or suggestion that the needless delivery method of Bellhouse would enhance the permeation of a subsequently administered therapeutic agent**

Appellants argue that nothing in either of the references suggests that the needless delivery method of Bellhouse would enhance the permeation of a subsequently administered therapeutic agent. Instead, Bellhouse merely discloses a method of delivering a therapeutic agent. The fact that the method is safe and quick, by itself, does not provide a motivation to combine the references. Accordingly, the Examiner's rationale does not provide any motivation to combine the Bellhouse method with a second method of delivering a therapeutic agent as disclosed in Eppstein.

In response to this argument, the examiner position is that the rational to modify or to combine the prior art does not have to be expressly stated in the prior art; the rational may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art. The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve different problem. It is not necessary that the prior art suggest the combination or modification to achieve the same advantage or result discovered by applicant. *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972). Eppstein teaches method for trans-membrane delivery comprising the step of making micropores to that membrane using non-invasive needleless method, followed by administration of a transdermal device. However, Eppstein does not teach using particles from a syringe to make the micropores. Bellhouse is relied upon for teaching non-invasive needleless syringe and particles that may contain the drug to safely and painlessly deliver active agents to the skin. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to provide a method for administering a therapeutic agent to the skin or mucosa comprising forming pores in the skin or mucosa using noninvasive means followed by topical application of the active agent by a patch as disclosed by Eppstein, and use the noninvasive needleless syringe disclosed by Bellhouse to form the skin pores, motivated by the teaching of Bellhouse that the needleless method is safe quick method with less pain and no risk of infection, with reasonable expectation of having a method for delivery of active agents across the skin or mucosa comprising porating the skin with needleless

Art Unit: 1615

syringe using particles followed by application of a topical device such a method accelerates the drug delivery through the skin or mucosa to the systemic circulation safely and quickly with no pain.

In the light of the foregoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the claims would have been *prima facie* obvious over Eppstein in view of Bellhouse within the meaning of 35 U.S.C. 103 (a).

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

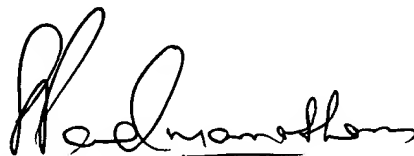
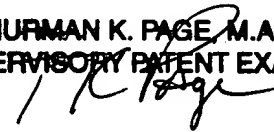
For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

IG *Iris Ghali*

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